REMARKS

Claims 1 to 40 and 42 to 53, as amended, appear in this application for the Examiner's review and consideration. Claims 1 to 32, 39, 40, and 46 to 53 have been withdrawn from consideration, as being drawn to non-elected subject matter. Claim 41 has been canceled without prejudice by this Amendment. The amendments are fully supported by the specification and claims as originally filed. Therefore, there is no issue of new matter. In addition, the amendments to the independent claims add recitations that elaborate on the structure of the presently claimed invention, and, thus, do not affect the scope of the claims. The amendments only further clarify the claimed invention.

Applicants wish to acknowledge with appreciation the courtesies shown to Applicants representative, Alan Force, Reg. No. 39,673, in a telephone conference with Examiner Morris on August 17, 2005. The arguments set forth herein are in accordance with that conference.

Claims 33 to 38 and 41 to 45 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement, for the reasons set forth on pages 4 to 8 of the Office Action.

In particular, the rejection is based on the possibility of a change in polymorphic state of a crystalline form of a compound during storage or tablet preparation. The Office Action, at page 5, states

> The specification lacks description of how the pharmaceutical composition can be prepared in order to maintain the particular compound of a particular form with the particular infrared and x-ray diffraction being claimed. Disclosure of x-ray diffraction patterns for the compounds and pharmaceutical compositions comprising the polymorphic forms are lacking in the specification. The specification has also not described how the stable form and composition's being claimed will be maintained and prevented from converting to other forms.

In response, Applicants respectfully submit that XRD and IR spectra are not provided, and there is no teaching in the specification on how to maintain a particular polymorphic form because a new polymorphic crystalline form of lansoprazole is not disclosed or claimed in the present application. The presently claimed invention is directed to a chemically stable lansoprazole composition. That is, the presently claimed invention is a lansoprazole, produced in a known process, that is then stabilized with the method of the invention, providing the chemically stable lansoprazole of the invention. As the present claims are not directed to a new polymorphic crystalline form, no XRD or IR spectral data are required. No

disclosure of how to prevent the lansoprazole of the invention from converting to a different polymorphic form is provided, because the invention is not directed to a polymorphic form.

At pages 1 to 3, the present specification discusses the instability of prior art lansoprazole. As will be understood by one of ordinary skill in the art, the instability of lansoprazole discussed in the specification is not a polymorphic instability. Instead, the instability discussed in the specification is a chemical instability. When prior art lansoprazole is stored or exposed to heat and humidity, a chemical change occurs, producing impurities in the form of different chemical compounds, not different polymorphic forms. At page 3, lines 1 to 11, the present specification states that during storage, prior art lansoprazole degrades, such that the concentration of lansoprazole decreases, resulting in discoloration. Degradation of a compound results from a chemical change, not a change in polymorphic form, as alleged in the Office Action.

Moreover, the present specification clearly teaches one of ordinary skill in the art how to make and use the invention, and the specification describes the claimed subject matter in such a way as to reasonably covey to one skilled in the relevant art that the Applicants had possession of the claimed invention at the time the application was filed.

In the first paragraph on page 7, the specification discloses the impurities that are formed in lansoprazole during storage. The impurities are further disclosed in Tables 1 and 2 on pages 13 and 14, respectively. Processes for preparing the presently claimed chemically stable lansoprazole are set forth in both the Summary and Detailed Description sections of the specification, and are particularly exemplified in Examples 2 and 3 on pages 12 to 14 of the specification. The superior chemical stability of the presently claimed chemically stable lansoprazole, compared to the prior art compound, is set forth in the aforementioned Tables 1 and 2.

Clearly, one of ordinary skill in the art would understand how to make and use the presently claimed invention from the present specification.

With respect to an alleged lack of description as to whether the pharmaceutical carriers are able to maintain the compound in the stable form claimed, one of ordinary skill in the art, from the present specification, would understand how to make and use the presently claimed pharmaceutical compositions. Pharmaceutical carriers, diluents, disintegrates, binders, giants, dyes, colorants, lubricants, excipients, and the like, useful in the invention, are set forth on pages 9 to 12.

Therefore, as the presently claimed invention is not directed to stable polymorphs, but, instead, is directed to a chemically stable lansoprazole composition, the present specification clearly teaches one of ordinary skill in the art how to make and use the claimed invention, and, thus, the claims meet the requirements of 35 U.S.C. §112, first paragraph. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. § 112, first paragraph.

Claims 33 to 38 and 41 to 45 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for the reasons set forth on pages 8 and 9 of the Office Action.

In response, Applicants submit that claim 41 has been canceled, thereby mooting the rejection of claims 33 to 35.

With regard to the recitation of "containing" in claims 42 and 43, during the August 17, 2005, telephone conference, the Examiner stated that the present claims were directed to a compound, and, thus, could not be open ended. Applicants understand this to mean that a compound has a specific structure that cannot be modified without changing the compound to a different compound.

In response, Applicants submit that one of ordinary skill in the art would understand that any given sample of lansoprazole contains lansoprazole, trace amounts of water and/or alcohol, and trace amounts of impurities. Even with the presently claimed chemically stable lansoprazole, it is practically impossible to remove all impurities, although the amount of any impurities in the presently claimed chemically stable lansoprazole increases significantly more slowly during storage than does the amount in prior art lansoprazole. Thus, one of ordinary skill in the art would understand that the "stable lansoprazole" of the present invention is actually a lansoprazole composition that may contain various impurities, including the sulfone and sulfide derivatives recited in claims 42 and 43. Accordingly, Applicants did contemplate the inclusion of other parameters not recited in the claims. However, to expedite the early allowance of the claims, Applicants have amended the claims to recite a "stable lansoprazole composition," which clearly may comprise traces of impurities other than those recited in the claims, and, thus, the present claims may be open ended, and meet the requirements of 35 U.S.C. § 112. As noted above, one of ordinary skill in the art would understand that the originally claimed "stable lansoprazole" included lansoprazole, water and/or alcohol, and other trace impurities, and, thus, the presently claimed stable lansoprazole composition is fully supported by the application and claims, as originally filed.

With regard to the recitation of sulfone derivative and sulfide derivative in claims 42 and 43, those terms are clearly defined in Tables 1 and 2 on pages 13 and 14 of the specification, respectively, and, thus, would be understood by one of ordinary skill in the art.

With regard to the alleged claiming in terms of use in claims 42 to 45, Applicants submit that those claims define chemical and physical characteristics of the presently claimed stable lansoprazole composition, when exposed to certain conditions of temperature and relative humidity. This is a recitation of properties related to the stability of the chemically stable lansoprazole composition of the invention, not a use, and the claims are not use claims.

Therefore, the claims particularly point out and distinctly claim the subject matter Applicants regard as the invention. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. §112, second paragraph.

Claims 33 to 38 and 41 to 45 were rejected under 35 U.S.C. §102(a), (b), and/or (e), as allegedly being anticipated by Vrečer et al., Farmacevtski Vestnik (Ljubljana) 1997, 48, pages 242 and 243 (Vrečer), Kotar et al., Eur. J. Pharm. Sci, 1996 4, page S182 (Kotar), WO 01/21617 to Choi et al., (Choi), U.S. Patent No. 4,628,098 to Nohara et al. (Nohara), U.S. Patent Application Publication No. 2004/0192923 to Singer et al. (Singer), U.S. Patent No. 6,002,011 to Kato et al. (Kato), and U.S. Patent Application Publications Nos. 2003/0036554 and 2004/0138466 to Avrutov et al. (Avrutov I and Avrutov II, respectively, and, collectively, Avrutov)) for the reasons set forth on pages 2 and 3 of the Office Action.

In response, Applicants submit that, as recited in claims 33 to 38, the presently claimed invention is directed to a chemically stable lansoprazole composition, prepared by the process of the invention. As recited in claims 42 and 43, the presently claimed invention is directed to a chemically stable lansoprazole composition, comprising less than about 0.1% (wt/wt) sulfone derivative and less than about 0.1% (wt/wt) sulfide derivative, upon exposure to a relative humidity of 75% at 40°C for a period of at least about three months and for a period of at least about six months, respectively. As recited in claims 44 and 45, the presently claimed invention is directed to a chemically stable lansoprazole composition that does not change color upon exposure to a relative humidity of 75% at 40°C for a period of at least about three months. Claim 41 has been canceled, mooting the rejection of that claim.

As demonstrated by Examples 2 and 3 of the present specification, the presently claimed chemically stable lansoprazole composition is substantially more chemically stable than prior art lansoprazole. After one month at a temperature of 40°C and a relative humidity

of 75 percent, none of the sulfone compound can be detected in the chemically stable lansoprazole composition of the invention, which remains white. In contrast, after one month under the same conditions, the non-stabilized, prior art lansoprazole contains 0.03 percent of the sulfone compound, and has changed color. Present specification, Example 2, pages 12 and 13. Similarly, after three months at 40°C and a relative humidity of 75 percent, the chemically stable lansoprazole composition of the invention contains only 0.03 percent of the sulfone compound, and remains white. In contrast, under the same conditions, the non-stabilized, prior art lansoprazole contains 0.06 percent of the sulfone compound, and has changed color. Present specification, Example 3, pages 13 and 14.

Although the cited prior art references may disclose lansoprazole and polymorphs of lansoprazole, the references disclose non-stable, prior art lansoprazole, not the presently claimed chemically stable lansoprazole composition.

In contrast to the presently claimed invention, Vrečer discloses the relative physical stability of polymorphic forms A and B of prior art lansoprazole. In particular, Vrečer discloses that lansoprazole polymorphic form B is not physically stable, and transforms to polymorphic form A on heating.

Vrečer discloses only non-stable, prior art lansoprazole, and, thus, Vrečer does not disclose a chemically stable lansoprazole composition, as presently claimed. Therefore, Vrečer does not anticipate the present claims.

Similarly, Kotar discloses the analysis of polymorphs of prior art lansoprazole, and that lansoprazole form B is not stable, undergoing a solid-solid transition to form A.

Kotar discloses only non-stable, prior art lansoprazole, and, thus, Kotar does not disclose the presently claimed chemically stable lansoprazole composition, and, thus, does not anticipate the present claims.

Choi discloses a process for preparing conventional prior art sulfoxide compounds, such as lansoprazole, comprising oxidizing a sulfide compound with hydrogen peroxide in the presence of a rhenium catalyst. The disclosed process reportedly minimizes the production of N-oxide and sulfone byproducts. Page 1, lines 4 to 17. The m-chloroperbenzoic acid, used in the prior art as the oxidizing agent, reportedly results in the formation of the N-oxide and sulfone byproducts, resulting in a low yield in the preparation. Page 3, lines 9 to 22. Other prior art processes, such as the oxidation of the sulfide compound with hydrogen peroxide in the presence of a vanadium catalyst, reportedly result in the production of more than 1 HPLC area percent of the sulfide compound and a product

containing 0.4% after purification. Page 6, lines 2 to 9, and page 7, lines 1 to 11. The disclosed process reportedly minimizes the production of the N-oxide and sulfone by products, and removes the by products by filtration.

Choi discloses a non-stable, prior art lansoprazole, and, thus, does not disclose the chemically stable lansoprazole composition of the presently claimed invention. Therefore, as Choi discloses a conventional lansoprazole, not the chemically stable lansoprazole composition of the present invention, the present claims are not anticipated by Choi.

Nohara discloses 2-[2 pyridylmethylthio-(sulfinyl)-] benzinidazoles and processes for preparing such compounds. A sulfide derivative, prepared with the disclosed process, can be oxidized to prepare a sulfinyl derivative. Column 2, lines 21 to 48. Compounds produced with the disclosed process "can be isolated and purified by conventional means, e.g., crystallization and chromatography." Column 2, lines 66 to 68.

Nohara discloses only non-stable, prior art lansoprazole, and, thus, does not disclose the presently claimed chemically stable lansoprazole composition. Therefore, the present claims are not anticipated by Nohara.

With regard to Singer, Applicants submit that that application is not prior art to the present claims. The Applicants of the present application are named inventors of Singer, and have assigned their rights to both applications to the same assignee. As evidence of Applicants' position, Applicants submit herewith (see Attachment 1) a Declaration under 37 C.F.R. §1.131 with the required supporting documentation.

Kato discloses a prior art, substantially solvent-free lansoprazole that is free of decomposition in the course of vacuum drying. Column 2, lines 22 to 26. Kato further discloses that, unless the lansoprazole is desolvated in accordance with the disclosed process, attempting to desolvate the compound by vacuum drying negatively affects the stability of the product. Column 1, lines 48 to 57, and column 2, lines 21 to 26.

Kato does not disclose a lansoprazole composition, having long term chemical stability, i.e., for over three to six months, as does the presently claimed chemically stable lansoprazole composition, which is stabilized by isolating and/or drying the lansoprazole composition in the presence of a relatively large amount of a weak base, such as ammonia. In Example 1, Kato discloses a process for the production of such a solvent-free lansoprazole in which 13 g of lansoprazole was crystallized from a solution comprising 75 ml of a 9:1 ethanol-water mixture and 70 μl of a 25 percent aqueous ammonia solution. As the molecular weight of lansoprazole is 363.97, 13g of that compound corresponds to 0.035

moles or 35 mmol. Assuming a density of from about 0.9 to 1 for a 25 percent ammonia solution, as the molecular weight of ammonia is 17.03, 70 μl of such a solution contains about 0.9 to about 1 mmol of ammonia. Therefore the amount of ammonia present in the solution of Example 1 is only about 2.6 to 2.9 mole percent of the amount of lansoprazole, i.e., a mole ratio of about 0.03:1. That amount is significantly less than the equimour amount presently claimed, and is not sufficient to provide the chemical stability of the presently claimed lansoprazole.

Similarly, in Comparative Example 1, Kato discloses crystallizing 10 g of lansoprazole from a solution comprising 58 ml of a 9:1 ethanol-water mixture and 54 μl of a 25 percent aqueous ammonia solution. Therefore, the amount of ammonia present is from about 0.71 to about 0.79 mmol, and the amount of lansoprazole is about 27 mmol, and, thus, the amount of ammonia is only about 2.6 to about 2.9 percent of the amount of lansoprazole, again, a mole ratio of about 0.03:1. Such a small amount of ammonia is not sufficient to provide the chemical stability of the presently claimed lansoprazole.

As discussed at page 2 of the present specification, the 0.03 moles of ammonia per mole of lansoprazole used in the Kato examples is only a trace amount, and is not sufficient to provide a chemically stable lansoprazole composition. As a result, the lansoprazole prepared by the processes disclosed by Kato will be chemically unstable during storage. Therefore, Kato does not disclose the presently claimed chemically stable lansoprazole composition, and, thus, Kato does not anticipate the present claims.

Avrutov discloses processes for preparing substituted 2-(2-pyridylmethyl)sulfinyl-1-H-benzimidizoles. Avrutov I and II, page 1, paragraph [0002]. In particular, Avrutov discloses a selective oxidation process for preparing lansoprazole. Avrutov I, page 2, paragraph [0016]; Avrutov II, page 2, paragraph [0025].

Avrutov discloses only non-stable, prior art lansoprazole. Therefore, Avrutov does not disclose the presently claimed invention, and the present claims are not anticipated by Avrutov.

Therefore, as none of Vrečer, Kotar, Choi, Nohara, Singer, Kato, and Avrutov disclose the presently claimed invention, the present claims are not anticipated by those references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. §102(a), (b), and/or (e).

Claimed 33 to 38 and 41 to 45 were rejected under 35 U.S.C. §103(a) as being unpatentable over the combined teachings of Vrečer, Kotar, Choi, Nohara, Singer, Kato, and

Avrutov in view of Hableblian et al., J. of Pharmaceutical Sciences, 1964, 58, pages 911-929 (Hableblian). Chemical & Engineering News, Feb. 2003, (C&E News), U.S. Pharmacopia, 1995, pp 1843-1844, Muzaffar et al., J. of Pharmacy (Lahore) 1979, 1(1), 59-66, (Muzaffar), Jain et al., Indian Drugs, 1986, 23(6), pages 315-329, (Jain), Taday et al., J. of Pharm. Sci., 92(4), April 2003, 831-838, (Taday), and Concise Encyclopedia Chemistry, page 872-873 (1993), for the reasons set forth on pages 3 and 4 of the Office Action.

In response, Applicants submit that none of the cited references disclose or suggest the chemically stable lansoprazole composition of the presently claimed invention.

As discussed above, Vrečer discloses the relative physical stability of polymorphic forms A and B of lansoprazole. In particular, Vrečer discloses that lansoprazole polymorphic form B is not physically stable, and transforms to polymorphic form A on heating. However, Vrečer does not disclose or suggest a chemically stable lansoprazole composition, as presently claimed.

Kotar discloses the analysis of the lansoprazole polymorphs, and that lansoprazole form B is not stable, undergoing a solid-solid transition to form A. Kotar does not disclose or suggest the presently claimed chemically stable lansoprazole composition.

Choi discloses a process for preparing conventional prior art sulfoxide compounds, such as lansoprazole, comprising oxidizing a sulfide compound with hydrogen peroxide in the presence of a rhenium catalyst. Choi discloses only non-stable, prior art lansoprazole, produced with the disclosed process, and, thus, does not disclose or suggest the presently claimed chemically stable lansoprazole composition.

Nohara discloses benzinidazoles and processes for preparing such compounds. The disclosed compounds are not the chemically stable lansoprazole composition of the presently claimed invention. Instead, Nohara discloses only non-stable, prior art, lansoprazole. Therefore, Nohara does not disclose or suggest the presently claimed chemically stable lansoprazole composition.

As discussed above and in the attached Rule 131 Declaration, Singer is not prior art.

Kato discloses a substantially solvent-free lansoprazole that is free of decomposition in the course of vacuum drying. Kato does not disclose or suggest a lansoprazole, having chemical stability over three to six months, as does the presently claimed chemically stable lansoprazole composition. The 0.03 moles of ammonia per mole of lansoprazole used in the Kato examples is only a trace amount, and is not sufficient to provide a chemically stable lansoprazole. As discussed above and at page 2 of the present specification, the lansoprazole

prepared by the processes disclosed by Kato will be chemically unstable. Therefore, Kato does not disclose or suggest the presently claimed chemically stable lansoprazole composition.

Avrutov discloses processes for preparing substituted 2-(2-pyridylmethyl)sulfinyl-1-H-benzimidizoles. Avrutov discloses only non-stable, prior art lansoprazole, and does not disclose or suggest the chemically stable lansoprazole composition of the presently claimed invention.

As stated in the Office Action at page 3, Hableblian, Muzaffar, Jain, and Taday each teach that some crystalline compounds can exist in different crystalline forms. The Office Action also states, at page 3, that C & E News, Muzaffar, U.S. Pharmacopia, and Concise Encyclopedia of Chemistry all teach that, at any particular temperature and pressure, only one crystalline form is thermodynamically stable.

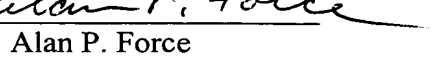
However, as discussed above, the presently claimed invention is directed to a chemically stable lansoprazole composition, not a thermodynamically stable polymorphic form. None of the cited references whether taken alone or in combination, disclose or suggest the presently claimed chemically stable lansoprazole composition. Instead, the cited prior art references discloses only non-stable, prior art lansoprazole.

Therefore, as the cited references, whether taken alone or in combination do not disclose or suggest the presently claimed invention, the claims are not obvious over these references. Accordingly, it is respectfully requested that the Examiner withdraw the rejection of claims 33 to 38 and 41 to 45 under 35 U.S.C. §103(a).

Applicants thus submit that the entire application is now in condition for allowance, an early notice of which would be appreciated. Should the Examiner not agree with Applicants' position, a personal or telephonic interview is respectfully requested to discuss any remaining issues prior to the issuance of a further Office Action, and to expedite the allowance of the application.

Respectfully submitted,
KENYON & KENYON

Dated: December 7, 2005

By: 

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